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SNAP-II score predicts outcome in congenital diaphragmatic hernia patients

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Abstract

Objective: Accurate and validated predictors of outcome for infants with congenital diaphragmatic hernia (CDH) are needed. Score for Neonatal Acute Physiology-II (SNAP-II) has been validated to predict mortality in newborns. We investigated whether SNAP-II scores in CDH could predict mortality, need for extracorporeal membrane oxygenation (ECMO) (in patients born in a centre with ECMO-availability), and development of bronchopulmonary dysplasia (BPD) (oxygen dependency beyond 28 days after birth) in survivors.

Design, setting: Data were obtained from a prospective, multicentre RCT of initial ventilation strategy carried out by the CDH EURO Consortium (NTR 1310).

Patients, interventions: CDH infants without severe chromosomal anomalies or severe cardiac anomalies born between November 2008- December 2013, were randomized for initial ventilation strategy (high-frequency oscillation/ conventional mechanical ventilation).

Measurements and main results: Logistic regression analyses were used to evaluate associations between SNAP-II score and outcome parameters. Of the 171 included patients, 46 (26.9%) died, 40/108 (37.0%) underwent ECMO, and 39/125 (31.2%) survivors developed BPD. In non-survivors, the median SNAP-II score was 42.5 (IQR 33.5- 53.8) and 16.5 (IQR 9.0- 27.5) in survivors ($p<0.001$). SNAP-II score also significantly differed between ECMO and non-ECMO treated patients ($p<0.001$), and survivors with and without BPD ($p<0.001$). Multivariable logistic regression analyses adjusted for hernia side, liver position, ventilation mode, gestational age, centre and observed-to-expected lung-to-head-ratio, showed that SNAP-II score was associated with mortality (OR 1.16 [1.09- 1.23], $p<0.001$), and need for ECMO support (OR 1.07 [1.02- 1.13], $p=0.01$), but not for the development of BPD (OR 1.04 [0.99- 1.09], $p=0.14$).

Conclusions: The SNAP-II score not only predicts mortality, but also need for ECMO in CDH patients. We, therefore, recommend to implement this simple and rapid scoring system in the

evaluation of severity of illness in patients with CDH and thereby have insight into the prognosis within one day after birth.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2200 live births(1). The defect in the diaphragm allows abdominal organs to “herniate” into the thoracic cavity, which leads to underdevelopment of both lungs, although more pronounced on the ipsilateral side. Lung hypoplasia and pulmonary hypertension are the main causes of respiratory failure and death. The aim of postnatal treatment is to prevent further lung damage by a gentle ventilation strategy and to stabilise the cardio-pulmonary status, followed by surgical repair of the defect. If conventional management fails, infants may require extracorporeal membrane oxygenation (ECMO) with a resulting survival of 51%(2).

Although the mortality rate has significantly decreased in the last decade to about 30%(3), CDH is still a life-threatening congenital anomaly(4). Various prenatal parameters are related to a worse prognosis, such as a low observed-to-expected lung to head ratio (O/E LHR), a right-sided hernia, herniation of the liver or stomach into the chest, and associated congenital malformations(5). Nevertheless, some neonates with prenatally expected poor outcome survive whilst neonates with prenatally expected good outcome die, those contradictions may be due to the inability to predict the pulmonary vascular response after birth. Reliable postnatal prediction models of survival and need of different treatment modalities in CDH infants are scarce. Recently, Brindle and colleagues published a prediction model based on postnatal baseline indicators and showed that this model could discriminate between high, intermediate and low risk of death(6).

The Score for Neonatal Acute Physiology, version II (SNAP-II score) is a prediction model used in newborns admitted to neonatal intensive care units and is based on six physiological parameters. SNAP-II score is a simplification of the original 28-items SNAP score(7). Some studies have shown that the SNAP-II score is related to worse outcome in

prematurely born neonates and infants with persistent pulmonary hypertension of the newborn(8, 9). In CDH patients, retrospective studies have shown that SNAP-II scores were higher in patients with a worse outcome(10, 11). The studies, however, included relatively low numbers of patients (47 and 88 patients) and one was performed before the introduction of a gentle ventilation strategy(10).

We have evaluated data collected in a multicentre, prospective randomized study comparing initial ventilation strategy(12). Our aim was to evaluate whether the SNAP-II score predicted mortality, need for ECMO, and development of bronchopulmonary dysplasia (BPD) in CDH infants. We hypothesized that higher SNAP-II scores would have been assigned to non-survivors, patients with need for ECMO, and survivors who developed BPD.

MATERIALS AND METHODS

Study design and population

Data collected in a randomized clinical multicentre trial were analysed(12). From November 2008 until December 2013, inborn neonates with prenatally detected CDH could be included in the trial. All parents gave prenatally written informed consent prior to inclusion in the study. The study was initially approved by the Erasmus MC Ethical Review Board (NTR1310) and the local institutional review boards provided institution-specific approval.

The study was conducted in nine tertiary, perinatal centres that all participated in the CDH EURO Consortium. High volume centres were defined as more than 10 CDH patients treated in one year. Exclusion criteria were: gestational age below 34 weeks; severe chromosomal anomalies likely to result in death in the neonatal period; severe cardiac anomalies with expected need of corrective surgery in the first 60 days after birth; renal anomalies associated with oligohydramnios; severe orthopaedic and skeletal deformities likely to influence lung development; severe anomalies of the central nervous system. We excluded

patients with a gestational age below 34 weeks so that the results could not be influenced by severe lung prematurity. Besides, a gestational age below 34 weeks is internationally considered a contraindication for neonatal ECMO-treatment due to the high risk of bleeding complications, in particular intracranial hemorrhage. After birth children were randomized to either initial conventional mechanical ventilation (CMV) or high-frequency oscillation (HFO). All children were treated according to a standardized neonatal treatment protocol(13).

The SNAP-II score was collected within the first 12 hours after birth, and comprises six physiologic parameters; mean blood pressure, temperature, (paO_2 (mmHg): FiO_2 (%)), serum pH, presence of multiple seizures, and urine output (Supplemental Digital Content 1)(7). For each parameter, the worst score within the first 12 hours of life was used to calculate the SNAP-II score, independent of possible treatment interventions.

BPD was defined as oxygen dependency at day 28 according to the definition of Jobe and Bancalari(14). ECMO support (in centers with availability of ECMO only) could be initiated if one or more of the following predetermined failure criteria were met for at least 3 hours at two consecutive measurements: inability to maintain preductal saturations above 85% (± 7 kPa or 52 mmHg) or postductal saturations above 70% (± 5.3 kPa or 40 mmHg); increase in $\text{CO}_2 > 65$ torr or mmHg (8.5 kPa) despite optimisation of ventilatory management; peak inspiratory pressure > 28 cm H_2O or MAP > 17 cm H_2O ; inadequate oxygen delivery with metabolic acidosis defined as lactate ≥ 5 mmol/L and pH < 7.20 and/ or hypotension resistant to fluid therapy and adequate inotropic support, resulting in a urine output < 0.5 ml/kg/hour; oxygenation index consistently ≥ 40 (12). None of the patients was transferred from a non-ECMO center to an ECMO center.

Data analysis

Patient characteristics are described as number (%), mean \pm SD or median (interquartile range; IQR). Survival rates of patients born in a centre with ECMO facilities and patients born in

a centre without ECMO facilities were compared using the chi square test. SNAP-II scores were compared between survivors and non-survivors, patients with and without need of ECMO treatment (in patients born in a centre with availability of ECMO only), and presence of BPD (in survivors only) using the Mann-Whitney U test. SNAP-II scores were compared between centres using the Kruskal-Wallis test. Independent associations between SNAP-II score and mortality, ECMO support (in patients born in a centre with availability of ECMO only), and BPD (in survivors only) were evaluated using univariable logistic regression modelling and were presented as odds ratio (OR) [95% confidence interval], *p*-value. In multivariable logistic regression analyses, SNAP-II score, gestational age, initial ventilation type, side of defect, centre, O/E LHR and position of the liver were included as independent variables. For BPD, ECMO support was also included as independent variable in the multivariable logistic regression analysis. The calibration of the multivariable logistic regression model was assessed using the Hosmer-Lemeshow goodness-of-fit test. Receiver operating characteristic (ROC) curves were used to evaluate the prognostic value of SNAP-II scores for mortality, need of ECMO support (in patients with availability of ECMO only), and development of BPD (in survivors only). Those data were presented as areas under the ROC curves (AUC); [95% CI]. All analyses were performed using SPSS version 21.0 for Windows. A two-sided *p*-value of <0.05 was considered statistically significant.

RESULTS

One hundred and seventy one patients were included in the analysis of which 108 (63.2%) were born in a hospital with ECMO facilities. Forty-six (26.9%) patients died, 40 of the 108 infants born in a centre with ECMO facilities received ECMO (37.0%), and 39 (31.2%) of the 125 survivors developed BPD (Figure 1) (Table 1). In six centers ECMO was available, two centers had no ECMO availability, and in one center ECMO was available from 01-01-2013

onwards. Twenty-seven patients (25.0%) of the patients born in a centre with ECMO facilities died versus 19 (30.2%) of the patients born in a centre without ECMO facilities, $p=0.46$.

The SNAP-II scores were not significantly different between centers (data not shown). The SNAP-II scores were not significantly different between the two ventilation groups (CMV (median 21.0 (IQR 10.0- 40.0)) and HFO (median 25.0 (IQR 14.0- 40.0)), $p=0.44$. Of the nine centers, five were high-volume centers and four were low-volume centers. The median SNAP-II scores were comparable in high-volume centers (median 23.0 (IQR 10.0- 37.0)) and low-volume centers (median 25.0 (IQR 16.0- 41.0)), $p=0.21$.

In non-survivors the median SNAP-II score was 42.5 (IQR 33.5 to 53.8) and 16.5 (IQR 9.0 to 27.5) in survivors ($p<0.001$). In the selection of the 108 patients born in a centre with ECMO facilities, the median SNAP-II score was 35.0 (IQR 30.0 to 46.0) in patients treated with ECMO and 16.0 (IQR 10.0 to 26.0) in patients without ECMO treatment ($p<0.001$). Survivors with BPD had a median SNAP-II score of 25.0 (IQR 21.0 to 35.0) versus 14.0 (IQR 7.0 to 21.0) in those without BPD ($p<0.001$). In a subgroup of patients who were treated with ECMO ($n=40$), 19 survived and 21 died. Of the 19 survivors, the median SNAP-II score was 32 (IQR 23- 44) and the median SNAP-II score was 40 (IQR 32- 51) for non-survivors, $p=0.04$.

Univariable logistic regression analysis showed that SNAP-II score was significantly associated with mortality (OR 1.11 [1.08- 1.15], $p<0.001$), need of ECMO support (OR 1.08 [1.05- 1.12], $p<0.001$) (in patients born in a centre with ECMO facilities), and BPD in survivors (OR 1.07 [1.04- 1.11], $p<0.001$) (Table 2).

Multivariable logistic regression analysis correcting for O/E LHR, defect side, liver position, type of ventilation, centre, and gestational age, demonstrated that SNAP-II score was significantly associated with mortality (OR 1.16 [1.09- 1.23], $p<0.001$), and need for ECMO support in patients born in a centre with ECMO facilities (OR 1.07 [1.02- 1.13], $p=0.01$). In the multivariable logistic regression analysis with correction for O/E LHR, defect side, liver position, type of ventilation, centre, gestational age, and adding the variable ECMO support, we found

that the SNAP-II score did not predict the development of BPD in survivors (OR 1.02 [0.97- 1.08], $p=0.46$) (Table 3). The p -values of the Hosmer-Lemeshow test were larger than 0.05, indicating an adequate model calibration.

Based on ROC analysis, SNAP-II scores predicted mortality (AUC 0.88; [0.82- 0.94], $p<0.001$), need for ECMO support (in patients born in a centre with ECMO facilities) (AUC 0.81; [0.72- 0.90], $p<0.001$) and BPD development in survivors (AUC 0.77; [0.68- 0.86], $p<0.001$) (Figure 2).

DISCUSSION

We have demonstrated in this prospective study on a large cohort of prenatally detected CDH patients that the SNAP-II score calculated within the first 12 hours of life predicted the outcome of survival, and need for ECMO support in inborn patients with CDH.

Skarsgard et al have assessed the ability of admission SNAP-II score to predict mortality in 88 infants with CDH born between January 1996 and October 1997 in the Canadian Neonatal Network database(10). This was a retrospective, multicentre study with patients selected based on the ICD-9 code (756.6) for diaphragmatic anomalies and included patients ventilated before the introduction of the gentle ventilation strategy. They found that SNAP-II predicted mortality with an OR of 1.06 and (AUC) of 0.76. In our study we found a comparable OR (1.11) and AUC (0.88). It is possible that the higher predictive value we found may be due to the greater homogeneity of our study population as compared to that of Skarsgard's report that derived from centers with different treatment protocols.

In 2001, The Congenital Diaphragmatic Hernia Study Group estimated disease severity in the first 5 minutes after birth in more than one thousand neonates with CDH (15). In that retrospective study, a prediction model based on variables obtained at the time of birth such as birth weight and 5-minute Apgar score was designed to estimate risks for populations and they

found that those variables were most useful in a predictive equation. It is not, however, clear whether those variables were obtained before or after intubation. More recently Schultz et al retrospectively investigated the Wilhord Hall/Santa Rosa prediction formula ($pO_2[\text{max}] - pCO_2[\text{max}]$) and showed that mortality in CDH patients could be predicted with that formula(16). They, however, included a relatively small number of patients and the infants were not treated according to a standardized treatment protocol. Subsequently, Baird et al compared three different prediction models in the same cohort of 94 infants(17). They showed that the prediction model of the Congenital Diaphragmatic Hernia Study Group predicted mortality best with an AUC of 0.85, followed by SNAP-II score (AUC 0.79). In addition, they concluded that gestational age did not improve the prediction model, which is consistent with our results. A limitation of their study is that not all the components of the SNAP-II score, for example lowest temperature, were not collected and the SNAP-II score was not routinely calculated and recorded.

In the study from Brindle and colleagues(6), postnatal variables were collected, including birth weight, 5-minute Apgar score, presence of chromosomal or major cardiac anomaly, and suprasystemic pulmonary hypertension. Their model identified infants at low, intermediate, and high risk of death. The data from the CDH registry, however, were obtained from voluntary participation which had potential selection bias. In future studies a combination of the SNAP-II score and the prediction model published by Brindle may further improve risk stratification of CDH infants. Chiu et al recently showed in 52 outborn CDH patients that SNAPPE predicted survival and need for ECMO well(18). In the SNAPPE score, however, Apgar score, birth weight and small for gestational age are also included which makes this score more time consuming to calculate. Moreover, in their study only outborn CDH patients were included whilst we only included inborn CDH patients.

We investigated the role of the SNAP-II score in the prediction of the need of ECMO. This was recently researched by Coleman and colleagues(11). In their retrospective study, they

found that in outborn CDH patients the SNAP-II score calculated within the first 24 hours after admission predicted the use of ECMO support with an AUC of 0.76. We calculated SNAP-II score prospectively in the first 12 hours after birth, hence our study population was more homogenous than that of the previous study(11) and found an AUC of 0.81. A prediction study based on blood gas analyses showed that infants with a $\text{PaCO}_2 > 60\text{mmHg}$ on the first arterial blood gas had a higher 90-day mortality rate and were more likely to receive ECMO(19). They, however, did not report the site of obtaining the blood samples (pre- or postductal) and they did not perform ROC curves so our results cannot be compared with theirs. Survival rates following ECMO found in the current study are comparable to those reported by Stevens et al(20). On the other hand, Downard et al reported that 12 of the 14 patients treated with ECMO survived, which means a high survival rate of 86% (21). In the study of Downard et al, however, 28% of the patients were outborn, which is associated with a favorable prognosis(22). Furthermore, our study population may have been more severely ill. Downard et al regrettably did not report parameters associated to survival such as gestational age, lung-to-head ratio and liver position (intrathoracic or intra-abdominal).

We also investigated whether the SNAP-II score predicted BPD in surviving CDH patients. To the best of our knowledge, this has not been done in previous studies. A large number of patients who were treated with ECMO subsequently died and many survivors who were treated with ECMO developed BPD (Figure 1). This could explain why SNAP-II score predicted development of BPD in survivors in the univariable logistic regression analysis, but not in the multivariable logistic regression analysis in which ECMO was added as independent variable.

In various reports of patients with CDH, other non-patient related factors were analysed for association with the outcome. For example, Nasr et al showed that in 140 infants location of delivery influenced the outcome(22). In our study all patients were inborn so a bias of severity of

illness due to location of birth did not influence our results. Grushka et al evaluated the effect of hospital case volume on the outcome in 121 CDH patients(23). They found that SNAP-II score was not significantly different for high compared to low-volume centers; this was confirmed in our study.

Our data were collected in a randomized clinical trial and the difference in initial ventilation strategy could be seen as a study limitation. SNAP-II score, however, was not significantly different between the two ventilation groups and the type of ventilation was not significantly associated with outcome in the multivariable logistic regression modelling. The optimal *initial* ventilation strategy was recently investigated(12). We have shown that independent of ventilation strategy, SNAP-II score reliably predicts outcome. Therefore we do not think that this has influenced our results. A limitation of the SNAP-II score itself is that one of the items concerns the presence of multiple seizures. It is known, however, that neonatal seizures can be very subtle so possibly some of the studied patients may have experienced unrecognized seizures in the first 12 hours after life(24). The strengths of the current study are that, besides initial ventilation strategy, all children were treated according to the same study protocol. Furthermore, all children were inborn, which means that information from birth onwards was available. A strength of the SNAP-II score is that data collection of the six scoring items takes only two to four minutes(7). Future studies should address whether the use of a combination of the SNAP-II score and other predictive (biochemical) markers such as lactate(25), troponinT(26), and endothelin-1(27), could further improve prediction of prognosis in CDH patients.

CONCLUSIONS

In conclusion, determining SNAP-II score in the first 12 hours after birth is a reliable, not time-consuming scoring system to predict outcome in antenatally diagnosed CDH patients with

a gestational age of more than 34 weeks. We, therefore, recommend to implement this simple and rapid scoring system in the evaluation of severity of illness in patients with CDH, to thereby obtain insight into the prognosis within one day after birth. For research purposes it can also be used to compare severity of illness to evaluate differences in outcomes between centers.

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FIGURE LEGENDS

Fig 1 Flowchart of included patients

ECMO: extracorporeal membrane oxygenation. BPD: bronchopulmonary dysplasia

a: total of patients that died: $n=46/171$ (26.9%)

b: total of survivors with BPD: $n=39/125$ (31.2%)

Fig 2 ROC curves

Receiver operating characteristic (ROC) curves

a: mortality b: extracorporeal membrane oxygenation (ECMO) c: bronchopulmonary dysplasia (BPD)